II. REMARKS

Formal Matters

Claims 18, 19, and 21-60 are pending after entry of the amendments set forth herein.

Claims 18-25, 27, 29-33, and 46 were examined and were rejected. Claims 26, 28, 34-45, and 47-51 were withdrawn from consideration.

Claim 20 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 52-60 are added. Support for new claims 52-60 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 19 line 24 to page 20, line 3. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Obviousness-type double patenting

Claims 18-25, 27, 29-33, and 46 were rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-5 of U.S. Patent No. 6,258,789, or claims 1-8 of U.S. Patent No. 6,225,290.

Applicants enclose herewith a terminal disclaimer, disclaiming patent term beyond the expiration date of U.S. Patent Nos. 6,258,789 and 6,225,290. Thus, this rejection of claims 18-25, 27, 29-33, and 46 may be withdrawn.

Rejection under 35 U.S.C.§112, first paragraph

Claims 18 and 20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description. Claims 18-25, 27, 29-33, and 46 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

Claims 18 and 20; written description

The Office Action stated that claim 20 "embraces a genus of altered protein relative to wild-type protein, and yet must exhibit applicant's intended utility, which is for use in a gene therapy protocol for correcting a disease or disorder in a mammal." Office Action, page 3.

Without conceding as to the correctness of this rejection, claim 20 is canceled without prejudice to renewal.

Claims 18-25, 27, 29-33, and 46; enablement

The Office Action stated that the specification does not reasonably provide enablement for the claimed invention as broadly claimed. The Office Action acknowledged that the specification demonstrates that administration of plasmid vectors expressing human insulin polypeptides into the gastrointestinal (GI) tract of rats suffering from diabetes reduces blood glucose levels in treated rats. The Office Action stated that the specification does not teach or provide sufficient guidance for one skilled in the art to reasonably extrapolate, without undue experimentation, from the efficacy of plasmid vectors expressing human insulin in suppressing the diabetic syndrome in streptozotocin-treated rats to methods of treating all other diseases or disorders in any and all mammals, wherein DNA encoding any and all other therapeutic proteins and/or wherein any other administration route is employed. Applicants respectfully traverse the rejection.

There is no requirement for a therapeutic effect recited in the claims, nor is there any statutory requirement to recite a therapeutic effect. Applicants have shown that a construct encoding insulin can be administered into a GI tract of a mammalian subject, with the result that the encoded protein is expressed in an intestinal cell, and is delivered into the bloodstream of the subject. Applicants have also shown that human growth hormone (hGH)-encoding DNA can be administered into a GI tract of a mammalian subject, with the result that the encoded protein is expressed in an intestinal cell, and is delivered into the bloodstream of the subject. Thus, the specification provides evidence that DNA constructs encoding **at least two different and distinct proteins** were successfully introduced into the GI tract of a mammalian subject, the proteins were expressed in an intestinal cell, and delivered into the bloodstream.

A specification which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter

sought to be patented must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). Even if a showing of therapeutic effect of the delivered protein were required, and Applicants submit it is not, the Office Action has provided no evidence that a therapeutic effect would not be achieved, using the methods of the invention. The Office Action acknowledged that a therapeutic effect was shown with the insulin-encoding construct. The Office Action has not provided any evidence or reasoning that a therapeutic effect would not be achieved with the hGH that was shown to be delivered into the bloodstream.

All one of ordinary skill in the art need to in order to practice the claimed invention is to (1) generate a construct comprising sequences encoding a secreted protein of interest, which is within the skill level of a skilled laboratory technician; (2) introduce the construct into a GI tract lumen of a mammalian subject, which can be accomplished as described in the specification; and (3) test a blood sample for the presence of the encoded gene product, as described in the specification, e.g., by ELISA, which is also within the skill level of a laboratory technician. Applicants do not dispute that one would have to test whether a given protein of interest were delivered into the bloodstream by application of the claimed method. Applicants submit, however, that the experimentation would be routine, and therefore not undue.

Comments regarding the cited art

The Office Action cited numerous references in support of the contention that the specification is not enabling. These references were cited as allegedly indicative of the "unpredictability of the art." None of these references has any relevance to the claimed invention. This is because none of these references describe gene therapy experiments which were conducted as disclosed and claimed, *i.e.*, administering a construct (1) not packaged into a viral particle (2) into the GI tract of a mammal. Instead, these references generally describe intravenous, intraperitoneal, or intramuscular administration of a gene construct, with the construct typically packaged into a viral particle.

Coghlan

The Office Action stated that Coghlan ((1995) *New Scientist* 148:14-15; hereinafter "Coghlan") (1) states that problems with gene therapy involve gene targeting and the number of genes reaching the target cells - estimated by some to be about 1%; and (2) discloses that even those genes which reach

their destination work inefficiently, producing too little protein for too short a time period to benefit the patient. As to the first point, it should be noted that *the instant invention as claimed does not involve or require gene targeting*. As to the second point, the relevance of the failure of others is unclear. *Coghlan does not discuss efforts to administer a construct into the gastrointestinal tract by oral administration*, as Applicants have done. Accordingly, Coghlan is irrelevant to the question of enablement of the instant specification. The present inventors clearly showed detectable levels of the expressed protein in the bloodstream, when the route of administration was into the GI tract. The Office Action has presented no evidence why one of ordinary skill in the art would not expect the instant methods to be successful, regardless of the protein-coding sequence being expressed.

The claims do not require treating a disease or disorder. The claims require that a gene construct be taken up by intestinal epithelial cells, the gene product expressed, and the gene product delivered into the bloodstream. Applicants have shown success with two different proteins: insulin and human growth hormone. *There is no statutory requirement for Applicants to show that the method will work for all possible gene products*. The Office Action further stated that the evidence obtained from the working examples is not "reasonably predictable" and correlated to a therapeutic effect in any or all subjects using the claimed method. Applicants do not understand this statement. Applicants have provided unequivocal evidence that the method as claimed was successfully applied to two different proteins. Why aren't two separate successful examples reasonably predictive that the methods could be successfully applied to other proteins? The Office Action has provided no evidence that one of skill in the art would doubt the truth of what Applicants have asserted, namely that the method can be applied to other proteins as well.

Ledley

The Office Action stated that Ledley ((1995) *Human Gene Therapy* 6:1129-1144; hereinafter "Ledley") teaches: "it is unlikely that any one method for gene transfer will prove to be effective in every organ. Rather, various formulations will need to be developed that can be used to deliver DNA to specific targets based on the biological properties of that target." *The instant invention as claimed does not require targeting any particular organ. There is no requirement in any of the claims for the method to be effective in every organ.* Furthermore, while Ledley discusses the promise of gene therapy by targeting tissues and organs such as lung, liver, endothelium, muscle, skin, and tumor masses, Ledley

does not describe any work in which a construct was introduced into the gastrointestinal tract of a subject such that the construct was taken up by intestinal epithelial cells. Thus, Ledley is not relevant to the instant invention as presently claimed.

Gunzburg

The Office Action stated that Gunzburg states that there are many problems to be overcome before gene therapy becomes a widely used treatment. However, whether a given method is "widely used" is not a criterion for patentability under 35 U.S.C.§112, first paragraph.

The Office Action stated that Gunzburg states that the efficiency of gene delivery is a limiting technical problem. However, whether a given method works efficiently is not a criterion for patentability under 35 U.S.C.§112, first paragraph.

Gunzburg discusses problems associated with viral gene therapy. Claims 19 and 33 depend from claims 22 and 28, respectively, which recite that the DNA construct is not contained within a viral particle, and that the DNA construct is naked. Accordingly, Gunzburg is not relevant to the instant methods as claimed.

Furthermore, none of the allegedly failed attempts to achieve gene therapy in humans discussed in Gunzburg used the instant methods as claimed. There is no discussion in Gunzburg of a method involving introducing a DNA construct into the GI tract. There is no discussion in Gunzburg of a method involving introducing a DNA construct not encapsulated in a viral particle. Accordingly, Gunzburg does not lead to a conclusion that the instant claims are not enabled.

Still further, Gunzburg states: "gene therapy shows much promise for the treatment of a diverse number of diseases that are currently poorly treatable, and it should be viewed with the optimism attributable to any new medical breakthrough." Thus, again, Gunzburg does not lead to a conclusion that the instant claims are not enabled.

Verma

The Office Action stated that Verma states that the problem with gene therapy is an inability to deliver genes efficiently and to obtain sustained expression. However, as noted above, efficiency is not a criterion for patentability under 35 U.S.C.§112, first paragraph. Nor is sustained expression. Furthermore, despite any and all negative implications in the art, Applicants demonstrated expression of genes delivered to the GI tract, and delivery of the encoded proteins to the bloodstream.

Wirtz

The Office Action stated that Wirtz et al. ((1999) *Gut* 44:800-807; hereinafter "Wirtz") teaches that intravenous or intraperitoneal injection of AdCMVbetaGal into healthy BALB/c mice caused strong reporter gene expression in the liver and spleen but not in the colon. Applicants note that the claims require introduction of a construct **into the gastrointestinal tract** of the subject. The claimed invention does not relate to intravenous or intraperitoneal injection of a construct. Accordingly, Wirtz is not relevant to the claimed invention.

Cryz

The Office Action stated that even with oral administration of immunogens and/or DNA vaccines, the state of the art exemplified by Cryz et al. ((1996) *Vaccine* 14:665-688) indicates that oral delivery of any vaccine to gastrointestinal cells remains unpredictable. The Office Action went on to state that a section authored by Davis teaches: "Effective delivery to the GALT is predicated with enormous problems" including low efficiency of uptake.

Applicants note that, as recited in the claims, the construct introduced into the gastrointestinal tract is taken up by intestinal epithelial cells. Gut-associated lymphoid tissues (GALT) lining the intestinal tract includes the Peyer's patches lining the small intestine. The intestinal epithelium overlying the Peyer's patches is specialized to allow the transport of antigens into the lymphoid tissue. This particular function is carried out by epithelial cells termed "M" cells, so called because they have numerous microfolds on their luminal surface. M cells absorb, transport, process and present antigens to subepithelial lymphoid cells. Thus, GALT is subepithelial lymphoid tissue. While these tissues may in fact take up the construct and express the encoded protein, *this is not a requirement of the claimed invention*. Applicants have demonstrated that it is the intestinal epithelial cells that take up the construct administered directly into the gastrointestinal tract. Thus, the teachings of Davis are irrelevant to the instant invention as claimed.

Doerfler

The Office Action stated that Doerfler ((1995) *Gene* 157:241-245; hereinafter "Doerfler") teaches that when naked DNA if fed orally to mice, "a small amount of this DNA transiently survives the digestive regime of the animals' GI tract, although in heavily fragmented form," and that "a minute proportion of the fed M13mp18 DNA can be retrieved from the bloodstream of mice between 2 and 8 h

after feeding, mainly associated with leukocyte population." The Office Action concluded that oral administration of viral vectors or nonviral vectors is not a predictable practice.

Doerfler's teachings actually support the notion that a construct can be administered directly into the gastrointestinal tract of a mammalian subject by oral administration. As the Office Action correctly noted, Doerfler teaches that a small proportion of double-stranded bacteriophage DNA administered orally to mice is not degraded and remains intact. Doerfler describes experiments in which mice were fed M13 mp17 double-stranded DNA (7250 bp) either in the circular or linearized form. Doerfler, page 244, column 1. Doerfler reported that fragments of the DNA about 900 bp in length were found in blood, and that fragments of over 1600 bp were found in feces. Doerfler apparently did not even coat the DNA with an enteric coating. Thus Doerfler does not indicate that double-stranded DNA does not reach the intestine following oral administration.

Anderson

The Office Action stated that Anderson ((1998) *Nature* 392:25-30; hereinafter "Anderson") summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make an impact on the treatment of diseases, and that several major deficiencies still exist, including poor delivery systems, both viral and non-viral, and poor gene expression after delivery.

Applicants are required to show only what is claimed. Applicants have shown that, after administering two separate constructs encoding very different proteins into the gastrointestinal tract of a mammalian subject, a gene product of each construct was found in the bloodstream of the subject. Applicants do not claim, and are not required to show, any particular efficacy. As to a "treatment of a disease," Applicants in fact did show that the amount of insulin secreted into the bloodstream was sufficient to reduce blood glucose levels in the animal.

The Office Action went on to state: "Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types." There is no statutory requirement that Applicants know how an invention works, only that they impart how to make and use the invention. Applicants have fulfilled the "how to make" and "how to use" requirements of 35 U.S.C. §112, first paragraph.

Moreover, the thrust of the Anderson article is that gene therapy holds great promise, that "in a time frame of 5-15 years from now, I expect the number of gene-therapy products will begin to increase

exponentially," and that non-viral gene delivery systems "will be the preferred choice in the future." In addition, Anderson does not discuss any experiments in which a construct was administered directly into the gastrointestinal tract of a mammalian subject, and a gene product of the construct was found in the bloodstream, as Applicants have done. Thus, Anderson does not support a conclusion that the instant specification is non-enabling for the full scope of the claims.

In conclusion, the above-cited references do not describe gene therapy experiments which were conducted as disclosed and claimed, *i.e.*, administering a construct (1) not packaged into a viral particle (2) into the GI tract of a mammal by oral administration. Accordingly, the above-cited references cannot support a conclusion that the instant specification is non-enabling.

Declaration of Dr. Stephen Rothman

Notwithstanding the above discussion, Applicants note that administration of a construct into the GI tract of a mammal by oral administration can be accomplished as described in the instant specification. As evidence of the fact that a construct can be administered directly into the GI tract of a mammal by oral delivery, Applicants provide herewith as Exhibit 1 a copy of the Declaration of Dr. Stephen Rothman, which was provided with the response to the Office Action which issued on November 23, 1999 in the parent case (U.S. Patent Application No. 09/254,988). The Declaration of Stephen Rothman provides further evidence of the fact that gastrointestinal tract administration by oral delivery can be accomplished by known, art-accepted methods. The Declaration demonstrations delivery by both (1) introduction into the duodenum; and (2) oral administration. The results were the same, regardless whether the construct is introduced by oral administration, by introduction into the duodenum, or by direct injection. Regardless of the route of administration, an introduced DNA construct enters an intestinal epithelial cell and is expressed therein. Accordingly, the specification is indeed enabling for oral administration of a formulation comprising a DNA construct not packaged in a viral particle into a GI tract lumen of a mammalian subject, wherein the construct enters an intestinal epithelial cell.

Applicants submit that the rejection of claims 18-25, 27, 29-33, and 46 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(e)

Claims 18-25, 27, 30-33, and 46 were rejected under 35 U.S.C.§102(e) as allegedly anticipated by Mathiowitz et al. (U.S. Patent No. 6,248,720; "Mathiowitz").

The Office Action stated that Mathiowitz teaches a method of orally delivering to a mucosal epithelial surface a DNA encoding an antigen or an insulin protein to a mammal, wherein the DNA is encapsulated in a polymeric capsule. Applicants respectfully traverse the rejection.

Comments regarding the art rejections

Before the rejection under 35 U.S.C. §102(e) is addressed, Applicants believe a few comments are in order.

Applicants made the surprising discovery that administering DNA, even naked DNA, directly into the GI tract of a mammalian subject leads to: (1) uptake of the construct by intestinal epithelial cells; (2) expression of the gene product encoded by the construct in these cells; and, perhaps most surprising, (3) delivery of the gene product into the bloodstream. The prior art had neither disclosed nor predicted that one would be able to detect in the bloodstream of a subject a protein encoded by a construct and introduced directly into the GI tract. One reason for the unexpected nature of these results is that the ability of intestinal epithelial cells to take up DNA is unexpected. The great majority of intestinal epithelial cells are absorptive cells, which are designed to function primarily in absorption of water, ions, and nutrients. Absorbed nutrients are those which have been broken down in the GI tract, and are carbohydrates, which are absorbed in the form of mono- and di-saccharides; proteins, which are absorbed in the form of amino acids or peptides; and fats, which are absorbed in the form of monoglycerides and free fatty acids. DNA is a macromolecule considerably larger than the molecules normally taken up at the apical surface of intestinal epithelial cells.

Furthermore, until Applicants' demonstration set out in the specification, it was not predictable that expression of a recombinant construct in an intestinal epithelial cell would result in delivery of the encoded polypeptide into the bloodstream. Intestinal epithelial cells are polarized, *i.e.*, they have a distinct luminal surface and a distinct basolateral surface. The intracellular trafficking signals that direct delivery of proteins produced within these cells are not completely understood, and one could not predict either the occurrence of or direction of export until the experiment is actually carried out. Thus, until applicants invention, it was not predictable, and thus unexpected, that recombinant proteins would be delivered out the basal cell surface and into the bloodstream. Delivery of a protein into the bloodstream was neither disclosed nor predicted by the prior art. Thus, it was unexpected that

recombinant proteins such as insulin and human growth hormone would be delivered out the basal gut epithelial cell surface and into the bloodstream.

Comments regarding inherency anticipation

According to the law, a reference may anticipate a claim even if a feature recited in the claim is not specifically disclosed in the reference. However, where the reference is silent as to a specific limitation in the claims (*e.g.*, secretion into the bloodstream), such a gap in the reference must be filled with recourse to extrinsic evidence in order for the reference to serve as an anticipatory reference by inherency. Such evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill in the art* at the time the invention was made.[1] The characteristic must flow *undeniably and irrefutably* from the express disclosures of the prior art reference. Mere possibilities or even probabilities are not enough to support a finding of anticipation.[2]

In relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art.[3]

Mathiowitz does not disclose or suggest a method of delivering protein into the bloodstream of a mammalian subject, the method comprising introducing into the gastrointestinal tract of a mammalian subject by oral administration a construct comprising a nucleic acid molecule comprising a coding sequence encoding a protein, wherein the construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell, production of the encoded protein in the intestinal epithelial cell, and delivery of the protein into the bloodstream of the subject.

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[1] *Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ2d 1746, 1749-1750 (Fed. Cir. 1991). In this case, a summary judgement of inherency anticipation was deemed improper because of a material fact issue whether a prior art reference's process *necessarily* produced the claimed invention's features.

[2] *Motorola, Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481 (Fed. Cir. 1997)

[3] *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd.Pat.App.& Inf. 1990)

Mathiowitz does not disclose delivery of a gene product into the bloodstream.

The Office Action, in stating that absent evidence to the contrary, the protein is secreted into the bloodstream, is making an assumption with no basis in fact. Such an assumption is tantamount to an argument that, given the teaching of Mathiowitz, the ordinarily skilled artisan would recognize (at the time of filing and without the benefit of the disclosure of the present specification) that it would undeniably and irrefutably flow from this teaching that the protein would be secreted into the bloodstream. As discussed in detail above, there are two requirements for showing anticipation by inherency: (1) a characteristic which the Office Action claims to be possessed by the system disclosed in Mathiowitz, i.e., secretion into the bloodstream, must *necessarily* be a characteristic of the system that would be recognized as such by the ordinarily skilled artisan at the time of filing; and (2) the Examiner *must provide a basis in fact and/or technical reasoning* to reasonably support the statement that the protein is secreted into the bloodstream. Neither of these requirements has been fulfilled.

Mathiowitz provides an example of introducing a construct encoding β-galactosidase (β-Gal) into the stomach. Mathiowitz, Example 4, column 24. Mathiowitz provides no disclosure whatsoever that the β-Gal protein was delivered into the bloodstream. There is no discussion of, and no data showing, delivery of β-Gal into the bloodstream.

Mathiowitz lists various genes to be delivered, including genes encoding viral antigens, tumor antigens, and cytokines. Mathiowitz, column 17, lines 32-50. However, Mathiowitz does not provide any showing of delivery into the bloodstream. Without a showing of secretion into bloodstream, a list that includes proteins that are active in the bloodstream is merely a wish list.

Mathiowitz fails to disclose each and every element of the instantly claimed invention. Mathiowitz does not show delivery of a gene product into the bloodstream of the subject. Accordingly, Mathiowitz cannot either explicitly or through inherency anticipate the instant invention as claimed.

Conclusion as to the rejection under 35 U.S.C.§102(e)

Applicants submit that the rejection of claims 18-25, 27, 30-33, and 46 under 35 U.S.C. §102(e) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF048CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 7, 2003

By: _____
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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